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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/084,826	02/24/2002	Alan P. Wolffe	8325-0014.20	4340

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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/084,826	WOLFFE ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10-36 and 40-73* is/are pending in the application.

4a) Of the above claim(s) *1-7, 10-33 and 44-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36 and 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response, filed 04/21/2005, amending claim 40. Claims 1-7, 10-36 and 40-73 are currently pending and claims 34-36 and 40-43 are under consideration in this action. As noted in the previous action, Claims 1-7, 10-33 and 44-73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 10/18/2004.

All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections/rejections repeated herein. As no new grounds of rejection are set forth, **this action is made FINAL.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 34-36 and 40-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

This rejection is of record and is repeated in its entirety herein. A response to Applicant's arguments is set forth immediately following the body of this rejection. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In particular, the claims are directed to a genus of fusion molecules having structures with a requisite functionality, i.e., DNA binding and enzymatic functionality. Therefore, the genus comprises two distinct structures where each structure is defined by a particular function (i.e. DNA binding domain (DBD) and enzymatic domain) as well as undefined functional fragments of the enzymatic component or of the remodeling complex. In addition, claim 40 encompasses non-protein fusion molecules where the DNA binding domain of the fusion molecule can be a chemical compound (e.g., interchelating agent), nucleic acids or proteins. As such, with respect to claim 40 the genus of fusion molecules is broadened even further.

Therefore claims encompass a large number of fusion structures that must have the requisite function of binding DNA and facilitating chromatin remodeling or performing the recited enzymatic functions (i.e. histone-methylase/demethylase, -kinase/phosphatase, -ubiquitinase, -ADP ribosylase or -protease) in any cell/organism. The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The specification discloses a fusion polypeptide comprising a DBD that recognizes target sequences in the human VEGF gene, which is alternatively fused to BAF155, MBD1, MBD2, MBD3, DNMT and KRAB. (e.g., Figs. 6-7; Examples 2-13).

However, none of the foregoing defined structures functions as a histone-methylase/demethylase, -kinase/phosphatase, -ubiquitinase, -ADP ribosylase or –protease. In addition, with regard to the disclosed structures no further clarification of potential functional fragments is provided, where for example, a single amino acid change could abrogate chromatin-remodeling functionality. As the specification points out, chromatin remodeling can occur through DNA or histone covalent modification. The disclosed embodiments are directed exclusively to DNA modification, while the claims encompass a genus that includes both DNA or histone covalent modification. There are no embodiments disclosed of structures or functional fragment of structures that function to covalently modify histones.

The specification provides guidance on assaying for chromatin remodeling, however such guidance could provide sufficient support for an enablement requirement, but are not sufficient support for the written description requirement. Moreover, "Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117). Furthermore, knowing that a product may exist, in the absence of what that product consists of (i.e. actual structure) is not a description of that product. (*University of California v. Eli Lily and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)). In sum, the specification fails to describe the structure of any enzymatic components that operate as a histone-methylase/demethylase, -kinase/ phosphatase, -ubiquitinase, -ADP ribosylase or -protease. In addition the specification does not describe the structure of any functional fragments of either the preceding histone modifiers or the disclosed structures (supra, Figs. 6-7; Examples 2-13).

The specification does not provide any structures comprising non-protein fusion molecules (e.g., genus of molecules encompassed by claim 40). Furthermore, knowledge in the art does supplement the instant disclosure's omission of a sufficient description. For example, "In contrast to the relative wealth of information about the large number of acetyltransferases and deacetylases, relatively little is known about the enzymes that generate other histone modifications". (Grant, P. Genome Biology. 2001; 2(4):1-6, p. 3, col. 2, ¶ 2). In addition, a vast number of other histone modifications await discovery or further investigation, which include ADP-ribosylation and ubiquitanation. (Id., p. 4, col. 2, last ¶). For example, a particular protein factor may be recognized as having a histone modifying activity, but the actual structure (i.e. enzymatic domain) for said activity would not necessarily be identified. (e.g., Pham et al. Science. 2000; 289:2357-60; showing histone ubiquitin activity for $TAF_{II}250$). In essence, the evidence in the art may recognize that certain histone covalent modifiers are out there, but the defined structure of such modifiers or functional fragments thereof is not known.

Given the enormous breadth of the fusion molecules, comprising DNA binding domains and enzymatic components or chromatin remodeling complexes, including functional fragments thereof, encompassed by the rejected claims, including non-protein-protein fusion molecules, and given the limited description in the instant specification of such fusion molecules, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to described the broadly claimed genus. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant presents arguments to address separately each portion of the claimed genus of fusion molecules. First, Applicant asserts that the existence, structure and properties histone methyltransferases, histone kinases, histone phosphatases, histone ubiquitinating and de-ubiquitinating enzymes and histone proteases are described in the instant specification. (Remarks, p. 11).

Second, Applicant asserts that sufficient structures of DNA binding portions are also described. In addition, Applicant asserts that there is no requirement that each and every sequence falling within the scope of the claims be set forth in the specification. (Remarks, p. 13).

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("The description must clearly allow persons of ordinary skill in the art to recognize that (the inventor) invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious" and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966. Further, the Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105).

The Guidelines further state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

Regarding disclosure of sequences/structures, Applicant is correct that there is no requirement that the sequence/structure for all embodiments to be disclosed or known. There appears to be a misapprehension regarding such a requirement, since no such requirement was set forth. Indeed, as is repeated in the body of the rejection above and stated in the Action mailed 01/21/2005, the written description requirement for the claimed genus of fusion molecules may be satisfied, if a sufficient description of a representative number of species of said fusion molecules is described, i.e., fusion molecule structures correlating to the function of targeted DNA binding *and* the requisite enzymatic activity of histone methyltransferases, histone kinases, histone phosphatases, histone ubiquitinating and de-ubiquitinating enzymes and histone proteases. Therefore, the issue is whether a sufficient number of fusion molecules are described and nucleotides encoding fusion polypeptides comprising a DNA-binding domain and an enzymatic component.

Regarding Applicant's assertions that written description is satisfied, it is respectfully reasserted that the specification fails to describe a sufficient number of fusion molecule structures.

Knowing a structure exists with a prescribed enzymatic activity, in the absence of what that structure consists of, is not a description of a structure. (*University of California v. Eli Lily and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)). Rather, to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("The description must clearly allow persons of ordinary skill in the art to recognize that (the inventor) invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious" and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966. Further, as the Guidelines for Written Description state:

> "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). The Guidelines further state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

The instant specification provides insufficient description of the essential/critical structures encompassed by the broadly claimed genus of fusion molecules. Notably, the specification identifies structures that are *non-enzymatic components* of chromatin remodeling complexes (e.g., MBD1, MBD2, MBD3, DNMT and KRAB; Examples 2-13, Figs. 6-7).

In other words, not a single embodiment is disclosed of a fusion molecule structure that functions to covalently modify histones. Further, the specification does not identify any fusion molecule, fusion protein or polynucleotide encoding a fusion protein that comprises or encodes a "functional fragment" of an enzymatic component.

In addition, the specification does not identify a single fusion molecule where the DNA-binding domain is a non-protein (e.g., chemical agent or nuclei acid), but that is linked to an enzymatic component or functional fragment thereof, and that effectuates chromatin remodeling. Moreover, the disclosure does not identify a common structural feature amongst the subgenus of the claimed Markush set of enzymatic components that correlates to the prescribed enzymatic functions that result in covalent modification of histones. In sum, there is a paucity of description in the specification regarding the description of a sufficient number of structures or description of a common structural feature that correlates to the prescribed enzymatic functions, or as to any clarification of structures that are "functional fragments" of the prescribed enzymatic components. Such a dearth of information is of particular concern where the genus/subgenus of fusion molecules/proteins can number in the hundreds, or thousands when considering the various sources of the enzymatic components.

Therefore, it appears one must rely entirely on the evidence in the art so as to envisage a sufficient number of the fusion molecules encompassed by the claimed genus. (e.g., Remarks, p. 11, last ¶, bridging to p. 12; citing Jenuwein et al. 2001; Hsu et al. 2000; asserting that even if examining a single example of the evidence in the art one of skill would deem written description as sufficient).

The cited art is not on point because the instant claims are not merely directed to a histone-remodeling enzyme, but rather to a fusion molecule comprising a targeting domain (e.g., chemical compound, nucleic acid or protein) and an enzymatic component (i.e., histone covalent modification) or functional fragment thereof. First, the evidence in the art simply does not provide identification of a sufficient number of "functional fragments" of the subgenus of enzymatic components encompassed by the claims.

Second, a handful of examples of enzymes having distinct structures/sequences and distinct enzymatic functions (e.g., biologically distinct covalent modification of histone H3, H4 or H1) does not explicitly or implicitly equate to such structures/correlated functions as being conventional and readily identifiable. Third, no common structural feature is identified as amongst the various subgenera each encompassing a distinct enzymatic activity (i.e., histone-methylase, -ubiquitination, -de-ubiquitination, -kinase, -phosphatase and –protease). In other words, the evidence in the art does not explicitly or implicitly suggest that enzymatic components, histone modification enzymes or functional fragments thereof, are *conventional* in the art. Nor does the evidence in the art suggest that fusion molecules comprising said enzymatic components are conventional in the art. It is not contested that histone covalent modification enzymes exist, as is evidenced by references of record. However, the instant specification lacks a sufficient number of representative structures and said insufficiency is not ameliorated by evidence in the art. Therefore, one of skill cannot deem Applicant to be in possession of the claimed genus.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action.

In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

DAVID GUZO
PRIMARY EXAMINER